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Using skin for drug delivery and diagnosis in the critically ill ☆

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ABSTRACT

Skin offers easy access, convenience and non-invasiveness for drug delivery and diagnosis. In principle, these advantages of skin appear to be attractive for critically ill patients given potential difficulties that may be associated with oral and parenteral access in these patients. However, the profound changes in skin physiology that can be seen in these patients provide a challenge to reliably deliver drugs or provide diagnostic information. Drug delivery through skin may be used to manage burn injury, wounds, infection, trauma and the multisystem complications that rise from these conditions. Local anaesthetics and analgesics can be delivered through skin and may have wide application in critically ill patients. To ensure accurate information, diagnostic tools require validation in the critically ill patient population as information from other patient populations may not be applicable.

Contents

1. Introduction

Critically ill patients admitted to the intensive care unit (ICU) are at a high risk of death and usually have multiple organ dysfunction related to severe acute illness. Management of these patients involves prompt resuscitation, establishment of a complete diagnosis, supportive care such as nutrition and maintaining fluid and electrolyte balance and specific treatment of life-threatening issues such as hypotension, hypoxaemia, hyperkalaemia, hypoglycaemia and dysrhythmias. These patients require careful monitoring both their general condition and their treatment response. Much of this management requires appropriate drug administration to achieve a desired clinical effect with a safe level of drug at the target tissue [1]. The range of drugs used in critically ill patients may include supportive therapy with sedatives,

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neuromuscular blocking drugs or analgesics and specific organ support or therapy with agents such as antibiotics, inotropes, diuretics, histamine H_2-receptor antagonists, bronchodilators and immunosuppressant drugs. Safety and efficacy of each drug will depend on both drug-related factors such as administration route, dose regimen, pharmacokinetic and pharmacodynamic characteristics of the drug, as well as patient characteristics such as age, weight, physiological conditions and disease status.

The most commonly used route for drug administration in critically ill patients is the intravenous route, since it normally guarantees complete absorption (i.e. 100% drug bioavailability), speed of onset and the desired duration of resultant effect can be managed using either bolus dosing or continuous infusion. However, the intravenous route can be associated with a significant risk of adverse drug effects in the ICU [2]. Switching to alternative routes of administration, such as the topical route, can, in principle, offer an opportunity to mitigate this risk if predicable, effective and reliable drug delivery can be provided. Skin, as a large organ, is a well-established route of drug administration, with products being delivered by topical application, transdermal delivery and injection via the skin into the underlying tissues, including the dermis, subcutaneous tissue, muscle, blood vessels and specific sites, such as the spinal canal. Topical application allows local drug targeting with minimal systemic effects and is mainly used for delivery of anti-inflammatory, anti-histaminic, antibiotics and analgesic drugs. It is also possible that drug delivery via the skin can enable systemic or organ specific delivery, when applied or injected into various body sites. As critically ill patients may have profound changes in skin perfusion and temperature, use of the skin as a portal for drug delivery can present challenges. However, skin may have potential benefits for drug delivery given the ready access and prolonged drug delivery that could be offered. For instance, skin provides for a gradual response due to the lag in absorption arising from crossing the stratum corneum barrier and a sustained effect for most delivery systems, including patches, which might be helpful in managing certain critically ill patients. This review will focus on recent developments and the application of skin for the drug delivery to critically ill patients. In addition, the usefulness of skin as a site for diagnosis in critically ill patients is discussed.

2. Overview of skin as a mode of drug delivery and diagnosis

2.1. Skin physiology and structure

Skin plays a vital role in maintaining homeostasis, defending against the invasion of microorganisms and providing protection from environmental attacks such as heat, chemicals and toxins. It has a large surface area (1.5–2 m^2) and accounts for 16% of total body weight. It is metabolically active and plays an important role in preventing thermal, physical, and mechanical injury, preventing water loss and UV damage, regulating body temperature, synthesizing vitamin D3, facilitating sensation and immunological surveillance [3].

Skin is composed of three structural layers: epidermis, dermis and subcutis (subcutaneous fat tissue) or hypodermis (Fig. 1) [4]. Hair (follicles), sebaceous, sweat and apocrine glands, and nails are appendages. Human skin varies in thickness (eyelids ~1 mm; soles of feet ~4 mm), hair follicle density and other characteristics according to age and site although the basic structure is consistent throughout the body. The epidermis (0.05–1.5 mm thick) is the outermost layer of the skin and consists of various cell strata (stratum basale, stratum spinosum, stratum granulosum and stratum corneum) in a progressive differentiation from cell formation to cell death and desquamation, with stratum corneum being much thinner in protected areas of the body like the scrotum, scalp and eyelids and much thicker in those regions of the body associated with environmental friction such as the palms and soles. In certain disease states, for example, psoriasis, skin can show an increased turnover and have a reduced barrier function compared to normal skin. In diseases such as ichthyosis skin has a slower turnover and provides a greater barrier. Skin is the main physical and chemical

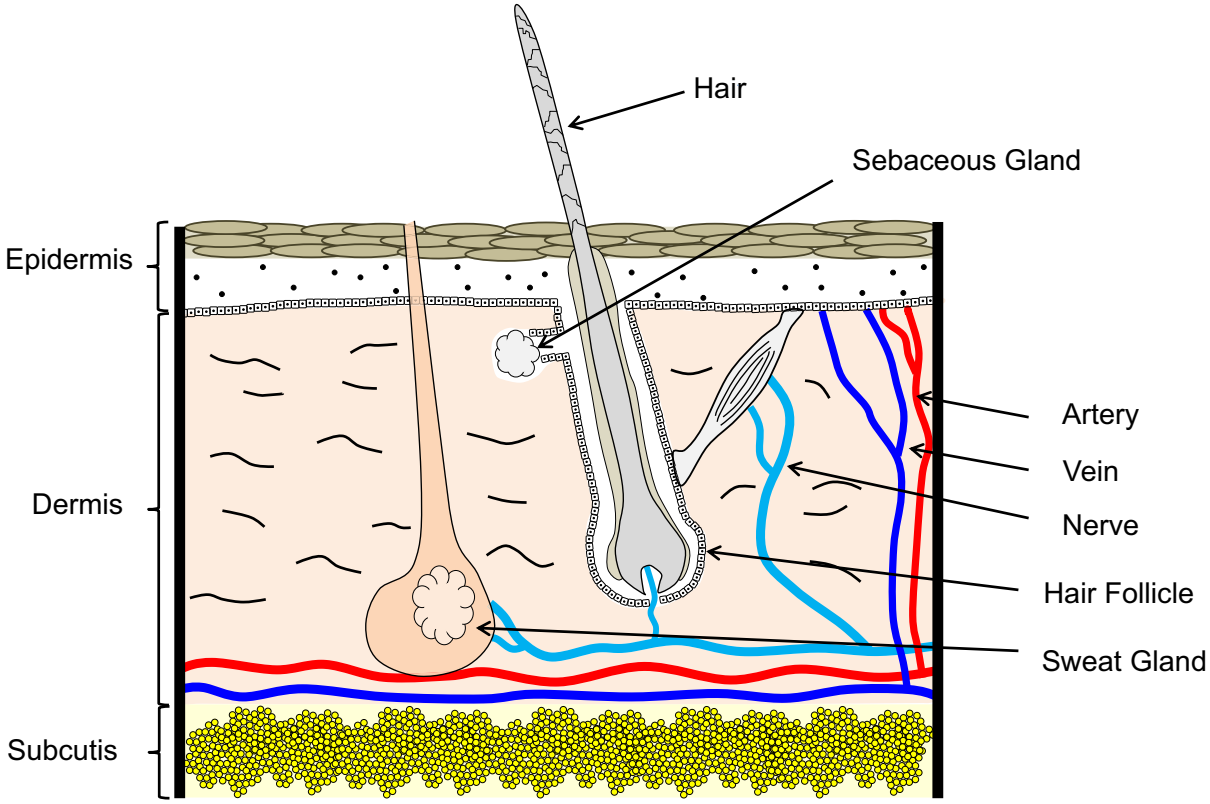

Fig. 1. A diagram of skin structure.

barrier protecting the interior body from the exterior environment. The dermis (1.1–2.3 mm) lies below the epidermis and provides structural vascular (blood and lymphatic vessels) and neural support for the skin. Drugs usually need to penetrate through the epidermis and reach dermis to enter systemic circulation. The subcutis or hypodermis (>10 mm) is below the dermis and is mainly composed of fatty tissue. It is the deepest layer of the skin anchoring the dermis to the underlying muscle or bone. The main function of this layer is to store fat and to carry blood vessels and nerves that supply skin. This basic structure is already in place in very preterm babies, with the exception being an underdeveloped outer layer of the epidermis, the stratum corneum. This results in an increase in insensible water loss, the passage of toxins such as alcohol more easily across the skin but also importantly increases the permeability of the skin to facilitate transepidermal migration of therapeutic substances.

2.2. Skin as a mode of drug delivery for both local action and systemic effect

Drug delivery through skin can be divided into topical delivery, transdermal delivery and subcutaneous injection. Characteristics of these routes are summarized in Table 1. Topical delivery is to apply a drug directly to skin and can be used for treatment of dermatological diseases via a large range of formulations including gels, lotions, creams, foams, and ointments. Topical drug delivery is also used for local anaesthesia, local infection management and photodynamic therapy [5,6]. These topically delivered drugs should reach the viable epidermis or dermis to take effect.

Skin is recognized as an attractive site for systemic drug delivery due to its large surface area, access convenience, and possibility of avoiding first pass metabolism in gastrointestinal tract and the liver. In addition, controlled zero-order drug release could be achieved through transdermal administration, which could reduce drug side effects or improve efficacy. Other advantages of transdermal drug delivery include ease of drug application and therapy cessation, important in the treatment of the critically ill patients. Further, a much longer duration of action is seen for drugs with a short elimination half-life given transdermally when compared with a dosing by an intravenous bolus. While this may be a positive in certain clinical circumstances, it also warrants caution for agents that require rapid titration to clinical effect in the critical care setting. A key challenge in transdermal drug delivery is overcoming the significant barrier to drug penetration provided by the outermost layer of the skin, the stratum corneum. This layer acts as the first line physical defence in preventing entrance of undesirable chemical and biological agents in the environment as well as in consumer and other products. It can vary widely in thickness from 10–20 μm for the back, arms, legs, and abdomen to 400–600 μm for plantar and palmar callus. It is composed of 10–30 flattened layers of 40 μm × 0.5 μm corneocytes (dead terminally differentiated keratinocytes) interwoven like a wall of very large, thin, hexaganol "bricks" set in intercellular lipids or "mortar" with a thickness between corneocytes of less than ~0.1 μm and, depending on the body region, pierced by sweat ducts and hair follicles. Thus, the transport of drugs across the stratum corneum could occur by one or more of three potential pathways: transcellular, intercellular and transappendageal pathways [7]. Whilst the intercellular lipids are highly structured and constitute a significant permeability barrier, it is generally considered the most favoured skin penetration pathway for most drugs [8,9].

Current available transdermal drug products are generally available as a patch or metered dose spray delivery and normally contain potent drugs (requiring 10 mg of drug per day or less) of moderate lipophilicity (logarithm of the drug's octanol-water partition coefficient, log P, 1–3), low molecular weight (usually less than 500 Daltons) and often with a low melting point [10]. These products typically contain drugs used for chronic conditions such as pain (e.g. fentanyl and buprenorphine), contraception (e.g. estradiol and norelgestromin), smoking cessation (e.g. nicotine), cardiovascular disease (e.g. nitroglycerin) and hormone replacement therapy (e.g. estradiol) and are formulated in patches, gels, metered dose spray, and ointment. Some have relevance to critical care either because chronic therapy may wish to be continued or of more interest would be their specific use in an acute illness (analgesics and nitroglycerin). Most appeared to be carried from the epidermis to deeper tissue by convective flow via protein binding in the cutaneous vasculature [11]. Whilst topical nonsteroidal anti-inflammatory agents are available and applied to the skin for local action in the deeper tissues below the skin, these products are rarely indicated in critical care medicine.

Subcutaneous drugs injected into the fatty subcutaneous tissue pass the epidermal and dermal layers of the skin and reach the systemic circulation via the capillaries or the lymphatic system depending on the drug molecular weight [12–14]. Absorption of various drugs from the injection sites can be affected by formulation characteristics (e.g. injection volume, ionic strength, viscosity and pH, and formulation excipients) [15], local degradation, cellular uptake, and precipitation or aggregation [13]. Extended drug absorption can be achieved by formulation modification or using sustained release formulations to provide prolonged exposure and reduced maximum plasma concentration.

Various anatomic sites can be used for subcutaneous injection including abdomen, upper arm and thigh which offers a broader range of options for multiple doses. The injection volume is usually small (1–2 mL). The most commonly studied subcutaneous injections include insulin, selected analgesics, heparin (including low molecular weight preparations such as enoxaparin, dalteparin), some other hormones (growth hormones, recombinant human erythropoietin), epinephrine and vaccine preparations. In critically ill patients, changes in skin physiology may affect drug absorption via subcutaneous route.

Deeper in skin, below the subcutis, is muscle and this has also been commonly used as an injection site. Intramuscular injection is often performed in the upper arm, thigh or buttocks. Injection volume can be larger than subcutaneous injection but has a limit of 2–5 mL depending on the injection site. Consistent with the higher blood perfusion of muscle, drug absorption after intramuscular injection is usually quicker than after subcutaneous injection. This may vary depending on the chemical properties of the drug. Emergency intramuscular administration of benzodiazepines can provide an effective and safe alternative to intravenous therapy in the early treatment of prolonged seizures [16]. Drugs administered intramuscularly include analgesics (e.g. codeine, morphine), sedatives (e.g. midazolam), antibiotics (e.g. penicillin, streptomycin), some hormones and vaccines. Intramuscular injection

Table 1
Summary of the characteristics of different drug delivery routes through the skin.

	Topical delivery	Transdermal delivery	Subcutaneous injection
Target skin layer	Epidermis or dermis	Viable epidermis or dermis	Subcutis (hypodermis)
Delivery mode	Local	Systemic	Systemic
Formulation	Gels, lotions, creams, foams, and ointments	Patches, gels, metered dose spray, and ointment	Solution
Medication	Treatment of skin disease; local anaesthesia; management of local infection; photodynamic therapy	Analgesia; smoking cessation; cardiovascular disease; hormone replacement therapy	Growth hormones; insulin; epinephrine
Limitation	Local effects	Skin permeability	Limited injection volume

is contraindicated in the setting of coagulopathy and as this may be relatively common in critically ill patients, the intramuscular route is of limited utility in the ICU. In addition, some drug preparations (e.g. diazepam) are irritant, which also prevents intramuscular injection.

2.3. Skin as a portal for diagnosis

Due to its ease of access, skin can also be used as the site for non-invasive diagnostic procedures (summarized in Table 2). Since ancient times several cardinal signs of inflammation are detected by skin examination. Rubor (redness), Calor (heat or warmth) and Tumor (swelling), to this day continue to represent a cornerstone of clinical medicine.

Simple physical examination of skin temperature using the dorsal surface of the hands or fingers of the examiner or using temperature-monitoring devices can serve as the indicator of peripheral perfusion. Cold skin could be associated with poor peripheral perfusion and impaired cardiac function [17]. However, skin temperature change can also relate to changes within local vascular beds only [18]. In this case, cool skin may only indicate vasoconstriction such as occurring in peripheral vascular disease and hypothermia [19]. Fingertip temperature estimates are also found to correlates well with objective measurements of fingertip blood flow [20]. Skin temperature monitoring has been used as non-invasive and inexpensive method of monitoring tissue perfusion and cardiovascular status in critically ill patients [21,22]. Body temperature gradient (core-to-peripheral) can reflect peripheral perfusion [23,24]. A fall in effective circulation blood flow decreases the heat conduction from the core, hence causes peripheral vasoconstriction and an increase in core-peripheral temperature ingredient. Skin may also provide earliest clue to an underlying systemic infection caused by various microbial agents such as viruses, bacteria and fungi by the classic changes on inflammation.

Skinfold thickness measurement, a simple method for quantitative assessment of the fat content of the human body, has been used in hospital and in general medical practice. It was first applied in as early as 1950s [25] and has gained popularity to measure body fat distribution [26–28]. Regression equations are developed in a large sample of people to relate the measurement of skinfold thickness to body composition (usually body density) for the prediction of the quantity of fat in the body [29]. These equations are only accurate in the population for which they were developed and would require cross-validation if a different patient population was of interest.

Bioelectrical impedance analysis (BIA) is a popular, non-invasive method for determination of body composition via the skin. Electrodes are placed on the hand, wrist, foot and ankle for the measurement. BIA was developed based on the understanding of tissue electrical properties that water and electrolyte-rich tissues such as blood and muscle conduct the current much better than fat, bone and air-filled space [30]. It can also estimate total body water and extracellular water in subjects without significant fluid and electrolyte abnormalities. BIA measures tissue conductivity proportional to electrolyte-containing fluid volume in the body and its response to a small alternating current [31]. Principles of BIA have been described in detail previously [32–34]. The applicability of BIA to the critically ill patient population remains unclear. Limitations due to significant acute fluids shifts in these patients, rapid alterations in electrolyte concentrations and the required precision for measurements in difficult clinical circumstances, all contribute to the potential inaccuracies.

Table 2
Summary of the application of skin as a site for diagnosis.

Measurements/Test	Diagnosis
Skinfold thickness	The fat content of the body
Bioelectrical impedance	Body composition (fat mass, total body water, etc.)
Hypersensitivity skin testing	Allergic rhinitis and asthma; food and drug allergy; stinging insect hypersensitivity
The tuberculin skin test	Latent and active tuberculosis infection
Pulse oximetry	Oxygen saturation
Pulse densitometry	Liver function
Cutaneous dialysis	Drug penetration through skin and drug level in tissue

As a portal for diagnosis, skin tests remain useful to identify agents that may have caused allergic reactions. Allergic reactions are common in the general population [35]. The critical care environment results in exposure to a wide range of the common potential allergens in medical practice; these include drugs (neuromuscular blocking drugs, antibiotics), antiseptic solutions (chlorhexidine) and latex. If an allergic reaction occurs in critically ill patients, follow up testing is vital to assist in identification of the precise causative agent so this can be avoided in the future. Compared to other blood tests (RAST, total IgE testing, Eosinophil counts) skin tests are rapid, simple and relatively non-invasive and safe. Immediate-type hypersensitivity skin tests can be performed by percutaneous route (skin prick, scratch and scrape test) pricking or scratching a few drops of diluted allergen onto the skin surface (usually the forearm) or by the intradermal route injecting a tiny amount of allergen into the dermis [36]. Intradermal tests, usually used for diagnosis of venom and penicillin allergy, are less specific but much more sensitive than percutaneous tests. Delayed-type hypersensitivity skin tests (patch skin tests) apply allergen containing patch onto the skin (usually on the back) for 48 hours and are usually used for diagnosis of contact dermatitis triggered by nickel metal, hair dyes, cosmetic preservatives, fragrances, or plants.

At present, the use of the skin as a portal for diagnosis and treatment in critical care is much less developed than in other disciplines such as in the diagnosis of cystic fibrosis by sweat chloride measured after pilocarpine iontophoresis and by sweat conductivity tests [37]. Recently, microneedle technology has also been used in combination with pilocarpine iontophoresis to increase sweat production [38]. Today, non-invasive biophotonic imaging (including confocal, multiphoton, interferometry, photoacoustic, Raman and various its forms) is widely being used to assess the skin penetration and disposition of nanoparticles in humans, skin metabolic status and the effectiveness of various topical therapies [39,40]. Whilst the evolution of these methods to critical care may seem to be a long way off, it is interesting that the electrical impedance technique developed to diagnose skin cancers [41] has recently been adapted for the electrical impedance tomography of the lung using multiple skin electrodes and used to observe and quantify intrathoracic ventilation-dependent gas distribution [42].

Skin can be used as a portal for various devices to monitor different parameters in patients. A pulse oximeter is a device that indirectly measures a patient's arterial oxygen saturation of haemoglobin via the skin. It has become standard of care in many clinical settings including the operation room, hospital wards, intensive care units and emergency departments. It uses the principle of plethysmography with a light collecting sensor to measure the absorption of red and infra-red light by pulsatile blood. The ratio of the absorption by oxygenated and deoxygenated haemoglobin is derived and this provides an insight into the percentage of haemoglobin saturated with oxygen (oxygen saturation). The clip-like probe is usually placed on finger or earlobe or an adhesive probe may be placed on finger or forehead and can provide data about pulse rate and quality. In addition to the use of pulse oximetry in neonatal ICU it has other applications such as for screening healthy newborn infants to detect desaturation not visible to the eye, in congenital heart disease [43] and in the fetus at risk of hypoxemia during labour [44]. This principle has been extended to another device for non-invasive measurement of liver function through the skin based on plasma disappearance rate of indocyaine green (ICG). LiMON (Impulse Medical System, Munich, Germany) has adapted pulse oximetry with different light wavelengths to allow the estimation of ICG disappearance.

Microdialysis is a minimally invasive technique to study biochemical, metabolic and pharmacological process in tissue by placing a small dialysis probe into a living tissue. Cutaneous microdialysis places the probe, a tubular semipermeable membrane, in the dermis or subcutaneous fat tissue and perfuses it with dialysate via afferent and efferent

tubing. Substances in extracellular space could permeate through the membrane and be collected in dialysate. This technique is often used to study drug penetration through the skin and to monitor drug level in the tissue [45]. Microdialysis may gain application beyond a research tool and evolve in daily critical care practice as both a monitoring tool and to guide drug dosing [46,47]. Linking pathophysiology, tissue levels and drug pharmacology can provide useful information that is likely to gain increasing acceptance in routine practice [48].

3. Skin for drug delivery in critical illness

3.1. Pathophysiological changes in critical illness

Critically ill patients often develop multiple organ dysfunction and this may require interventions such as renal replacement therapy, vasopressor support or intravenous fluid therapy, all of which can alter drug pharmacokinetic properties and affect drug delivery. Fluid shifts caused by increased capillary permeability and reduction of oncotic pressure could lead to significant increase in volume distribution of hydrophilic drugs. Drug protein binding changes in critically ill patients due to the decrease in albumin concentrations and increased α_1-acid glycoprotein synthesis, and this can affect drug volume of distribution. Change of drug clearance is usually associated with liver and kidney function and blood flow changes. Dysfunction of the microcirculation is common in critically ill patients and can result in multiple organ failure [49]. During circulatory failure, body blood flow is diverted from the skin to more vital organs such as the heart, brain and kidney, resulting in a decrease in skin perfusion [22]. Decrease in skin blood flow could affect drug absorption in transdermal drug delivery or after subcutaneous injection. The alterations in organ function and body fluid distribution can further impact on subsequent local or systemic pharmacology following initial dermal absorption.

3.2. Topical delivery for local action

Topical delivery is mainly used for achieving local effect and several examples exist of its utility in the critically ill.

Patients with major burns, perhaps the most serious of all skin injuries, often require critical care and infection is a significant risk. Topical therapy is commonly used in these patients to minimize the chances of wound sepsis, treat infection and promote a moist wound environment to prevent wound progression [50,51]. Silver sulfadiazine cream, an effective antibacterial agent, is one of the standard topical treatments [52] and has been used since 1960s [53]. The cream formulation can maintain the concentration of silver at effective level around the wound site for long time, thus reducing application frequency. New formulations of silver sulfadiazine based on nanotechnology have recently been developed to overcome some disadvantages of the cream, such as formation of pseudo-eschar and inflammation caused by the cream base [54], and to accelerate burn-wounds regeneration [55]. Silver nanoparticles have unique properties of high ratio of surface area to mass and have shown excellent antibacterial activities [56]. Wound dressings containing nanocrystalline silver have recently being introduced for burn management [57]. This formulation has been suggested to provide a sustained release of elemental silver and have a greater effect on preventing burn infections compared with silver sulfadiazine [58,59]. The topical delivery of silver nanoparticles was found to be effective in promoting healing of burn wounds with less scar [60]. However, its clinical application need to be further investigated prior to more widespread clinical use.

Topical antimicrobial therapy may have role in management of infected wounds related to pressure ulcers, vasculopathy or trauma, all of which can occur in critically ill patients. The advantages of topical delivery antimicrobial compared to systemic antibiotics include better efficacy in selected wound types and limited systemic toxicity due to less systemic absorption. High concentrations and sustained release of antibiotics at the infection site can be achieved, which may reduce the dose of antibiotics and potentially reduce chances of antibiotics resistance. Topical delivery may offer a wider choice of novel drugs which are not suitable for systemic delivery [61]. However, disadvantages of topical antimicrobial such as local hypersensitivity or contact dermatitis reaction, interference with wound healing processes and the potential alteration of normal cutaneous flora should also be considered. For patients with systemic illness complicating wound infection, systemic antimicrobial therapy may be required either in addition or in place of topical treatment. Antimicrobials suitable for topical delivery usually have a specific antimicrobial spectrum for particular wound infection, are potent with a rapid and sustained antibacterial effect and a low likelihood of developing bacteria resistance [61]. Commonly used topical antimicrobials include antiseptics, disinfectants and antibiotics with specific cell target. Some of these agents may have multiple microbial targets but also potential toxicity to skin cells such as fibroblasts and keratinocytes. Antibiotics available only as topical formulation are preferred for treatment of wound infection as those antibiotics also available for systemic therapy may induce delayed hypersensitivity reaction or develop bacteria resistance.

A pressure ulcer is a localized injury to the skin and is a risk for all critically ill patients, particularly in the setting of severe sepsis or shock, spinal cord injury, major trauma or malnutrition [62]. Statins may be a promising additional treatment of pressure ulcer due to their pleiotropic effects (e.g. anti-inflammatory, anti-oxidative, antibacterial, immune-modulatory) and prognostic impact on wound healing [63]. Topical delivery has been shown to be effective in wound healing of diabetes mellitus-induced foot ulceration in rats [64,65]. A Recent study from one hospital ICU has shown that long term (14 days) topical application of 1% atorvastatin ointment could accelerate and lead to complete wound healing of pressure ulcers in critically ill patients [66]. Further multicentre studies are necessary to confirm this result and elucidate the mechanisms of topical statins in treatment of pressure ulcer in various clinical settings.

Another application for topical therapy in critically ill patients is to reduce bacteria skin colonization prior to surgery, percutaneously inserted catheters, or other medical procedures. Topical antiseptics such as chlorhexidine gluconate, povidone iodine and alcohol are usually applied for this purpose although other compounds such as colistin, octenidine, and tea tree oil may have some efficacy. Bacterial density on skin was found to correlate with chlorhexidine gluconate concentration after daily bathing in ICU patients [67] and the benefit of reducing bacteraemia and tolerance of daily chorhexidine bathing was observed in critically ill children in a multicentre, randomized and crossover trial [68]. Recent research done by Climo et al. [69] evaluated effects of daily chlorhexidine washcloth bathing in ICU patients and found reduced risk of acquiring multi-drug resistant organisms hospital acquired blood stream infection. Effect of daily bathing with octenidine was also reported in ICU [70]. The observed colistin resistance after prophylactic topical colistin application in ICU [71] serves as a reminder of the potential adverse impact that may result from widespread use of some antimicrobial agents, even with topical application.

Peripheral venous access is often difficult in critically ill patients due to pathophysiological conditions such as hypothermia, vasoconstriction or hypotension [72]. Central venous access may be required in these patients either for monitoring or administration of particular agents not suited to peripheral venous administration. Despite this peripheral venous access still has a role and is a common procedure in the ICU. Venodilation using topical nitroglycerin ointment as an aid to percutaneous venous access was reported three decades ago [72–74]. Its safety and efficacy has been demonstrated in healthy volunteers and patients undergoing surgery and it continues to be described as an adjunct for difficult intravenous cannulation or clinical situations to improve cutaneous blood flow [75,76]. Potential adverse haemodynamic effects of systemic nitrate absorption may limit its utility in the ICU. Although, if the ointment is only applied to the skin of the dorsum of the hand for

short time (~2 min), then is completely wiped off it will still distend the superficial veins but avoid systemic side effects such as hypotension and headache [76]. Interestingly some of the topical local anaesthetic preparations provide a degree of venodilation, although this was not their primary intention [77].

Topical anaesthetics used to numb the skin can control and relieve the pain associated with minor burns, lacerations, or other dermatological procedures such as skin biopsy or hair removal. Topical anaesthesia can be achieved via various formulations including gels, sprays, creams, ointments and patches. After topical application, the drug needs to penetrate through epidermis and reach the nerve endings within the dermis to take effect. Therefore drug effect will depend on the thickness of epidermis and its own physiochemical properties, especially the lipophilicity which determines how well the drug can penetrate skin barrier. Lidocaine, tetracaine or benzocaine, are the most commonly used topical anaesthetics applied on mucous membranes or other sites with ready rapid absorption. The anaesthetic formulation EMLA® (Eutectic Mixture of Local Anaesthetic) is a mixture on Lignocaine and Prilocaine. It provides effective analgesia through intact skin and has been for percutaneous vascular access and selected minor skin operative procedures [78]. Amethocaine (Tetracaine) has also been used in various formulations and mixtures to provide effective analgesia through intact skin [77,79].

For critically ill patients, topical anaesthesia may be utilized to reduce the pain for arterial, venous or urinary catheterization and some minor surgical procedures [80]. Current clinical practice in adults would more commonly involve administration of local anaesthesia by direct subcutaneous injection rather than topical or transdermal delivery. Future research may provide opportunity to further explore the place of topical anaesthesia in some of these patients.

3.3. Transdermal delivery for systemic effect

In contrast to the purpose of topical delivery for local effect, transdermal delivery aims to deliver drugs through the skin to achieve systemic effect. The opioids have remained non-replaceable drugs for pain control in the critically ill patients. Although intravenous administration is more commonly used in critically ill patients with acute pain, transdermal delivery of opioids has been attempted to block pain at peripheral sites with minimum central nervous system effects. In addition, transdermal delivery allows sustained release of drug over a prolonged period while maintaining a constant dosing. This is especially suitable for management of chronic conditions. Transdermal opioids cause less constipation compared to oral or parenteral opioids and prevent post-surgical ileus in varying patient populations and this may be applicable to the critically ill [81]. Buprenorphine is an opioid analgesic with a wide application in clinical practice for more than 30 years [82]. It is particular suitable for transdermal delivery due to its high lipophilicity, low molecular weight and high potency. Clinical trials indicate that transdermal patch of buprenorphine could provide greater pain relief, improve sleep quality, and decrease need for rescue therapy when used for management of moderate to severe cancer pain [82]. Fentanyl is another opioid possessing many physiochemical properties (e.g. high lipophilicity and low molecular weight) suitable for transdermal delivery. Transdermal fentanyl patches are used frequently for management of chronic pain and its application was initially studied in the postoperative setting in the early 1990s [83–85]. There are two types of fentanyl transdermal patches: the reservoir transdermal device and the matrix patch. The reservoir transdermal device is made of four functional layers: the first polyester film backing layer preventing leakage of patch contents onto surrounding skin; the second drug reservoir layer containing fentanyl and ethanol in a hydroxycellulose gel; the third ethylene vinyl acetate copolymer rate-controlling layer regulating the delivery rate of fentanyl to the skin surface and the last silicone adhesive layer providing a non-irritating and secure contact area with skin. The newly introduced matrix patch consists only two functional layers (polyester film backing layer and a silicone adhesive layer containing fentanyl) with a protective peel strip. Both patches show similar clinical pharmacokinetics and effects [86].

Limitation of transdermal delivery for critically ill patients is that the absorption of drugs may be affected by disease status resulting in erratic, unpredictable and possible inadequate absorption. Sometimes, the increases in skin temperature such as during the fever can enhance drug the absorption of transdermal applied drugs possibly due to increased drug solubility or cutaneous blood flow [87,88]. In addition, the application of skin patches may be problematic in critically ill patients when skin is damaged (e.g. in the case of major trauma or burns). Patches may not adhere well when patients are sweating, febrile or when skin is moist as is often the case in critically ill patients.

Transdermal delivery for the critically ill newborn offers several opportunities. Firstly, intravenous access may be difficult. Gut immaturity or immotility are often present and result in variable absorption of oral medications. The thinness of the strata corneum in the preterm infant offers particular opportunities for rapid tranCsdermal absorption. Despite these obvious opportunities there has been limited research and even more limited uptake of transdermal delivery. Sophisticated models of neonatal skin are available using microtones and pigskin with various amounts of strata corneum removed to represent different stages of skin development [89].

Variability of thickness of the stratum corneum and rapid postnatal development may mean that passive transdermal delivery results in variable drug concentrations, useful delivery of theophylline by this method has been described [90]. Other drugs have been identified where transepidermal absorption can be effectively controlled using iontophoresis. These include ranitidine where therapeutic neonatal doses can be easily achieved with the use of iontophoresis to simple gel patches of practical surface area (0.2 cm2/kg) and phenobarbitone [91].

Drug research has been hampered in the paediatric population both by the pharmaceutical industry being driven by profit rather than clinical need and the regulatory environment [92]. However, recently legislation has been passed in Europe and the USA to encourage the pharmaceutical industry to study medicines in the paediatric and neonatal populations. Whilst only 0.2% of the drug trials registered in the Clinicaltrials.gov database involve neonates, The number has increased 6-fold between 2000 and 2013 [93]. These developments provide new reason to explore mode of delivery, particularly transdermal delivery, in this group with the biological advantage of thin skin, and high clinical need.

3.4. Subcutaneous injection

Skin infiltration (subcutaneous injection) is another way of deliver drugs. Decreases in skin blood flow that may accompany critical illness can affect drug absorption following subcutaneous injection. Local anaesthetic subcutaneous injection was reported to be more effective at reducing pain caused by arterial punctures than topical applied anaesthetics [94]. Subcutaneous injection of opioids is a common practice to control severe postoperative and cancer-related pain. Opioids that can be delivered through subcutaneous administration include morphine, hydromorphone, pethidine, oxycodone and fentanyl. The subcutaneous route is an effective alternative to intravenous administration and has the advantages of easy application and relative less cost. It may also provide a depot of drug and so reduce the frequency of intermittent administration required or be useful for gradual weaning from analgesic or sedative drugs after prolonged sedation. Subcutaneous administration may reduce the need for intravenous access. This could “free up” existing intravenous access to allow more ready administration of other intravenous agents and may even facilitate the more timely removal of intravascular devices in selected patients [95].

One drug commonly injected subcutaneously in critically ill patients is heparin (both unfractionated and fractionated) used as prophylaxis for venous thromboembolism. Reduced systemic bioavailability of

subcutaneous low-molecular-weight heparin, can arise with vasopressor induced impaired peripheral circulation in intensive care patients [96]. It is possible that vasoconstriction or vasopressor therapy in critically ill patients can delay or reduce subcutaneous absorption. Low-molecular-weight heparin enoxaparin has also been found to have less anti-coagulation effect in critically ill patients with normal renal function after a single subcutaneous dose compare with general medical patients [97]. Consequently, a higher dose of subcutaneous low-molecular-weight heparin would be required in such patients to obtain the same factor Xa activity. Krishnamurthy et al. recently reported the reduced absorption of oxycodone after a single subcutaneous dose in critically ill patients and suggest dose regimens developed in healthy volunteers should not be directly translated to this population [98].

It might also be expected subcutaneous oedema to could result in reduced systemic absorption following subcutaneous injection. However, a study of dalteparin given subcutaneously to patients with and without oedema (defined as at least a 10% increase in body weight and the appearance of generalized oedema) did not show significant changes in either the peak anti-factor Xa heparin level and the area under the anti-factor Xa heparin level-time curve [99]. In a review of this literature, Crowther and Lim reiterate that a "potential mechanism by which critically ill patients may be predisposed to antithrombotic failure is the inability to achieve 'prophylactic' anticoagulant drug levels as a result of impaired absorption." [100]. Their summary suggests that an increased dose of anticoagulant would be needed when the patient is on a vasopressor but, until such time as adequately powered data shows otherwise, not necessarily so in critically ill patients with edema.

Specific circumstances exist where subcutaneous therapy may be more effective than conventional care in intensive care patients. One example is in the management of opoid induced constipation, where therapeutic options include conventional enteral products such as sodium picosulfate or glycerin suppositories and more recently the subcutaneous injection of the peripheral opioid antagonist methylnaltrexone. In a small retrospective study, a laxation occurred within 24 h for 86% of patients given a subcutaneous injection of methylnaltrexone compared to none of patients given conventional enteral therapy as a rescue treatment for gastrointestinal stasis in the ICU [101].

Blood sugar control has become a fundamental issue in the care of the critically ill [102]. Hyperglycemia can develop in hospitalized patients even without a history of diabetes and is associated with increased mortality in patients with acute myocardial infarction [103] and with trauma [104]. Glucose control in the intensive care unit has become the current practice recommendation [105] and a continuous intravenous insulin infusion is the preferred method due to the concerns regarding altered or unpredictable systemic absorption following subcutaneous injection in these patients. Glycaemic control in the critically ill has been the subject of much debate in recent years and shown in large scale randomised trials to influence patient outcome [106]. Intravenous insulin administration in critically ill patients requires frequent blood glucose monitoring to ensure both efficacy and safety [107]. Subcutaneous intermediate or long-acting insulin therapy might represent an alternative in selected patients to reduce frequency of blood glucose monitoring. The efficacy and safety of transition from intravenous regular insulin therapy to subcutaneous intermediate or long-acting insulin therapy have been demonstrated in critically ill trauma patients receiving continuous enteral nutrition [108] . Recently, the feasibility of automated closed-loop insulin delivery using the subcutaneous continuous glucose monitor has been investigated in critically ill adults [109].

In the critically ill and particularly the preterm infant, these same issues of hypoglycaemia and need for insulin infusion also occur. However a more common problem in the newborn is hypoglycaemia which occurs when the constant source of glucose via the placenta is removed at the time of birth. Transdermal absorption of glucose 40% gel across the buccal mucosa is effective in treating all but the more severe forms of this condition which, if not treated effectively, can result in brain injury [110].

Critical illness is associated with a vast array of potential immunological changes and further research is required to elucidate the impact of these changes on the route of administration and efficacy of vaccine effectiveness when administered to critically ill patients. Choosing skin immunisation sites involves consideration of feasibility, safety, efficacy to target skin antigen presenting cells and the capacity to induce long-term protection [111]. The two main sites of vaccination (muscle and subcutis) do not directly involve the skin-resident antigen presenting cells and can involve injections of 1 mL or more. The dermal route involves much smaller doses (100–200 μL) and directly involves the skin-resident antigen presenting cells and may enable the same response for delivery of about one hundredth the dose [112]. However, whilst some of the delivery systems used for this delivery is still at an early stage of development, the intradermal route is now being widely used for common vaccination procedures [113]. It is recognised that the elderly may present challenges for intradermal vaccine dosing because of their weakened immune response [114] and similar issues may exist for critically ill patients.

4. Skin for diagnosis in critical illness

Skin temperature monitoring as an indicator of tissue perfusion can be performed during examination of critically ill adults and children and maybe a useful adjunct to basic clinical examination and more sophisticated monitoring. The work by Ibsen in the 1960s [23] showed the relationship between skin temperature and cardiovascular status, which led to the understanding that the drop of skin temperature, especially big toe temperature, was a marker of peripheral vasoconstriction in patients with shock. The use of skin temperature and core-peripheral temperature gradients for haemodynamic assessment has been thoroughly reviewed by Schey et al. recently [115] to examine evidences of its application in critically ill patients. Caveats may need to be applied following cardiac surgery as hypothermia and cardiopulmonary bypass may alter the physiological responses in the peripheral circulation. However the use of differential skin temperature could be integrated into the haemodynamic assessment of critically ill patients. It has been suggested it warrants investigation in large-scale prospective studies [115].

Addressing nutritional requirements is also central to the care of the critically ill [102] and may influence both morbidity and mortality. Nutritional screening is difficult in critically ill patients. Skinfold thickness alone fails to identify multiple factors reflecting nutrition status and in critically ill patients maybe masked by tissue oedema or injury. Skinfold thickness can be combined with mid-arm circumference (MAC) to give the value of mid-arm muscle circumference (MAMC) and while this may be used as a nutritional marker to assess muscle mass and protein energy malnutrition [116], it also has limitations in critically ill patients.

Changes in lean tissue or body fluid partitioning in severely ill or injured patients may have prognostic significance. Methods to detect changes in body composition and the distribution of body water in these patients may offer new insights into pathophysiology and facilitate the better titration of fluid and drug therapies. Although there are quite a few techniques available for measuring body composition and water content, including radioactive isotope dilution, dual-energy X-ray absorptionmetry and hydrodensitometry all are difficult to apply in a clinical setting. Bioelectrical Impedance Analysis (BIA) has gained interest due to its non-invasiveness, low cost and easy accessibility. Application of BIA measurements in the clinical management of critical illness and the comparison with other methods for assessing body composition or body water distribution has been investigated [117,118] although the utility and reliability is yet to be established. The accuracy and reliability of BIA can be affected by nutrients, hormones, electrode placement, cation shifts, and cell membrane composition and fluidity. Disease states can also change the tissue conduction of electrical current. Therefore, equations developed in healthy

population are likely not relevant for the critically ill patients as the assumptions around fixed tissue hydration is violated [119]. While new equations, parameters and criteria have been explored to improve the accuracy of BIA in patients with alteration in water metabolism, oedema or at malnutrition states these have not been validated in critically ill patients [120,121].

Avoiding hypoxemia is a common goal in caring for critically ill patients and as such the continuous monitoring oxygen saturation, usually done by pulse oximeter, is an important standard of care. Conventional pulse oximetry was initially marketed in 1982 for use in the operating room. Because body movement severely affect the accuracy of measurement, it may not be suitable for all patients [122]. New technology such as Signal Extraction Technology [123] has been developed in an attempt to improve performance of oximetry in the ICU setting. The new generation of oximeters enables more accurate, effective and faster measurement of oxygen saturation in various clinical situations in critically ill adults and newborns [124].

The LiMON® (Pulsion Medical Systems, Munich, Germany) method has been used in critically ill patients for non-invasive measurement of ICG elimination by pulse spectrophotometry. The clinical value of the obtained parameter from LiMON measurement, ICG plasma disappearance rate (ICG-PDR), may be of prognostic value in patients with [125], liver failure after hepatectomy [126], and decompensated cirrhosis [127]. Non-invasive measurements of ICG-PDR using LiMON has been demonstrated to be reliable and results from critically ill patients have correlated with values derived from invasive fiberoptic-based method [128] and serial blood sampling method [129].

In critically ill patients, cutaneous microdialysis may be used as a monitoring strategy [130,131], especially for monitoring antibiotic levels at target site [132,133]. Subcutaneous tissue concentration of antibiotics obtained from microdialysis have been used gain insight into pharmacokinetic alterations that accompany critical illness and in attempts to achieve appropriate target site concentration in critically ill patients [134]. This method has also been applied to determine cortisol [135], glucose [136], linezolid [137], and levofloxacin [138] levels in interstitial tissues of critically ill patients. Microdialysis can be used to reflect organ or tissue blood flow and metabolism in a variety of clinical circumstances in the critical care unit such as neurotrauma [47,139] or following liver transplantation [140,141].

Transcutaneous gas analysis for both oxygen and carbon dioxide has been described for many years. It has been shown to be of potential use in the neonatal ICU likely due to the fundamental differences in skin structure seen with this age group [142]. It has not gained widespread use in adult critically ill patients for several reasons including thicker stratum corneum "blunting" the responses, concerns around the impact of altered tissue blood flow, the time and invasive sample requirement for calibration and the lack of well-defined threshold values for clinical decision making. It has been shown to have unacceptable wide variability in patients with respiratory failure requiring non-invasive ventilation [143]. New technologies such as near-infrared spectroscopy have shown similar variable results with altered tissue perfusion and the circulation changes seen in critical illness [144].

5. Conclusion

Skin provides a convenient portal for diagnosis and drug delivery. Although the inherent structure and barrier function provide a biological challenge to be overcome. Pathophysiological changes associated with critical illness further increase this difficulty. With the development of new formulation technology and techniques, these barriers may be overcome and thus increase the application of drug delivery to the skin. The advantage of using skin for both a delivery and diagnostic portal lies in its convenience of access and non-invasiveness. This may be of benefit for critically ill patients who often require of multiple and continuous monitoring of various parameters. Diagnostic tools need to be properly validated in the critically ill patient population before their application. Studies of drug delivery into or through the skin need appropriate PK/PD analysis, this could equally apply to agents such as heparin that are already in common use, to ensure appropriate dosing and clinical effect.

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